Treatment of Spastic Cerebral Palsy by Local Injection with Botulinum-A Toxin

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Abstract

Objective: To evaluate the efficacy of local intramuscular injections of three different doses of botulinum-A Toxin (Lantox) in the management of the spasm of cerebral palsy.

Method: 120 cases of children with cerebral palsy were divided into three average groups: group 1, group 2 and group 3. Three different doses of Lantox (group1, 1μ/lg; group2, 2μ/kg; goup3, 3μ/kg) were administered. The effect of treatment was evaluated by 'PRS' method. The difference between each group was calculated by 'analysis of variance'. The tolerance to Lantox and the side effects were also assessed.

Result: Reduction on spasm of muscle became apparent after injection (100%). Larger quantity of Lantox (2μ/kg, 3/μkg) is more effective than that of less quantity. No major side effects occurred.

Conclusion: Lantox may prove a simple safety and effective for the treatement of the cerebral palsy.

Key words: Botulinum-A toxin; Cerebral palsy; Treatment

Pediatric cerebral palsy is common in China and the rate of occurrence is 2% in infants. It is a difficult disease to be treated. Botulinum toxin type A can reduce and relieve the spasm of cerebral palsy, improve muscle balance and movement and avoid surgical operation. However, the experience of treatment of spasm of cerebral palsy by Botulinum toxin type A is not adequate. Poisoning may result if apply too much or the treatment result is not ideal if too little is applied. Drug tolerance may also developed if too many repeated doses. The most suitable dosage is important to be adjusted and controlled.

Method

1. Information

120 children with cerebral palsy were chosen after consented by their parents. The

patients were divided into three average groups. Group1 had 40 cases with 28 males and 22 females; averagely 5.9±2.6 years old (1.5 to 11.3 years old); 15 with single limb palsy, 14 with double lower limbs palsy, 15 with hemiplegia, 3 with double lower limbs and one upper limb palsy, 3 with four limbs palsy. Group 2 had 40 cases with 31 males and 19 females; averagely 7.2±3.1 years old (1.6 to 12.5 years old); 17 with single limb palsy, 8 with double lower limbs palsy, 19 with hemiplegia, 6 with double lower limbs and one upper limb palsy. Group 3 had 40 cases with 26 males and 24 females; averagely 6.2±3.9 years old (2.3 to 14 years old); 8 with single limb palsy, 11 with double lower limb palsy, 16 with hemiplegia, 6 with double lower limbs and one upper limb palsy and 9 with four limb palsy. Myograph excluded the possibility of myogenic disease.

2. Drug

Lantox, 100U/vial from Lanzhou Institute of Biological Products.

3. Methodology

3.1 Pre-treatment preparation

All patients stayed at hospital. Stool, urine, blood examinations and liver and kidney function examination were performed. Electrocardiography, electroencephalography, skull CT or MRI examination were done. Pre-injection motion evaluation was done by PRS (Physician Rating Scale) method. PRS scores were compared between groups. The result showed that there is no significant difference of PRS between each groups. (Group 1 and group 2: T=0.31, P=0.17; Group 1 and group 3: T=0.11, P=0.20; Group 2 and group 3: T=1.03, P=0.07).

3.2 Injection Method

The patients were laid down without anesthesia. After local disinfection, the operator will find the spasmodic muscle using his hand. In some cases, spasmodic muscle was not easy to identify. It will be localized by ultrasonic B and performed multi-point injection. Injection dosage: Group 1, 1μ/kg; Group 2, 2μ/kg; Group 3, 3μ/kg. The dosage for each group of muscle for one side and two side palsy were the same. The largest dosage should not exceed 6μ/kg for one time of injection. Adrenaline, trachea tube and respirator should be ready during operation. After injection, the patients were observed in hospital for at least five days. Blood pressure, breathing, pulse, heart rate, muscle strength, muscle tension and mental condition were observed in this period.

4. Efficacy Evaluation and Follow-up Study

Outpatient return visit were conducted after two weeks, one month, three month and

six months of injection, and PRS scores taken. The drug efficacy was proved when the treatment result could last for at least two weeks counted from the first few days with motion improvement.

5. Statistical Analysis

Use PRS (Physician Rating Scale) method for scoring. The scores were compared between four groups before and after injection and with three different dosages applied. P-value was calculated by F-test using SPSS.

Result

1. All the 120 cases of children have different extends of improvement after treatment. The effective rate was 100%. The time for the drug to take effect was 46±22 (21-75) hours after injection.

2. Group 1 (1μ/kg): 4 out of 6 criteria (talipes equines, back foot, back knee, walking speed) has no obvious improvement (Table 1). Group 2 (2μ/kg): back knee and walking speed had obvious improvement comparing with treatment before (Table p2). Group 3 (3μ/kg): all the six PRS criteria had improvement (Table p3).

3. Follow-up result: after one month, the treatment result was better than at the two weeks time. There was no significance difference for the treatment result at the times of two month and one month (Table 2 and 3). In three month's time, the treatment result of gait of group 1 and talipes equines of group 2 decreased but there is no larger change for other criteria. At six month's time, the number of follow-up cases in group 1, 2 and 3 were 31, 23 and 26 respectively and other follow-up cases lost. Except walking speed, other criteria were decreased, especially for gait of group one was obvious and more obvious for doing exercise. Within the 120 cases, the duration of treatment for the 20 cases of children, who were under two years old, was longer than that of other older children cases.

4. No anaesthetic or tranquilizer was used during the treatment and no side effect occurred during injection or post-injection.

Table 1. PRS score comparison before and after Lantox treatment by different dosage after two weeks

Items	n	Before (x±s)	Group1 (x±s)	Group2 (x±s)	Group3 (x±s)	q	P1	P2	P3	P4	P5	P6
Flection	40	0.66±0.82	0.87±0.73	1.31±0.61	2.03±0.63	36.32	0.00	0.03	0.02	0.07	0.05	0.00
Talipes equines	40	1.74±0.45	1.80±0.52	2.17±0.66	2.30±0.76	3.31	0.78	0.62	0.02	0..06	0.00	0.07
Back foot	40	1.22±1.02	1.23±1.12	1.66±1.10	2.31±0.53	9.87	0.11	0.05	0.00	0.21	0.00	0.05
Back knee	40	1.44±1.09	1.62±1.23	1.83±1.12	2.10±0.53	7.03	0.01	0.02	0.00	0.30	0.02	0.12
Walking speed	40	0.72±0.83	0.83±0.67	1.31±0.79	1.39±0.76	3.32	0.26	0.00	0.05	0..06	0.01	0.28
Gait	40	0.64±0.78	0.80±0.33	1.92±0.61	2.22±0.67	32.95	0.00	0.00	0.00	0.26	0.01	0.12

Remarks: P1: comparison of before treatment and group1; P2: comparison of before treatment and group2;
P3: comparison of before treatment and group3; P4: comparison for group 1 and group2;
P5: comparison for group1 and group3; P6: comparison for group 2 and group3.

Table 2. PRS score comparison before and after Lantox treatment by different dosage after one month

Items	n	Before (x±s)	Group1 (x±s)	Group2 (x±s)	Group3 (x±s)	q	P1	P2	P3	P4	P5	P6
Flection	40	0.66±0.82	0.96±0.81	1.66±0.77	2.22±0.71	40.60	0.00	0.00	0.00	0.05	0.00	0.00
Talipes equines	40	1.74±0.45	1.80±0.73	2.12±0.92	2.42±0.52	8.01	0.70	0.17	0.00	0.04	0.00	0.06
Back foot	40	1.22±1.02	1.62±1.12	1.82±1.02	2.36±0.83	11.73	0.03	0.00	0.00	0.32	0.00	0.01
Back knee	40	1.44±1.09	1.80±1.03	1.98±1.00	2.26±0.85	5.93	0.07	0.01	0.00	0.37	0.02	0.16
Walking speed	40	0.72±0.83	1.00±1.03	1.64±0.98	2.18±0.94	9.92	0.40	0.00	0.02	0.06	0.04	0.08
Gait	40	0.64±0.78	1.78±0.76	1.94±0.65	2.14±0.67	43.97	0.00	0.00	0.00	0.27	0.01	0.17

Remarks: P1: comparison of before treatment and group1; P2: comparison of before treatment and group2;
P3: comparison of before treatment and group3; P4: comparison for group 1 and group 2;
P5: comparison for group 1 and group 3; P6: comparison for group 2 and group 3.

Table 3 PRS score comparison before and after Lantox treatment by different dosage after two month

Items	n	Before (x±s)	Group1 (x±s)	Group2 (x±s)	Group3 (x±s)	q	P1	P2	P3	P4	P5	P6
Flection	40	0.66±0.82	0.93±0.78	1.57±0.61	2.31±0.72	40.60	0.05	0.03	0.00	0.05	0.05	0.00
Talipes equines	40	1.74±0.45	1.71±0.72	2.21±0.81	2.32±0.68	8.03	0.70	0.11	0.00	0.04	0.00	0.02
Back foot	40	1.22±1.02	1.25±1.12	1.76±1.05	2.39±0.48	11.33	0.09	0.06	0.00	0.32	0.00	0.01
Back knee	40	1.44±1.09	1.69±1.13	1.91±1.06	2.17±0.65	5.15	0.01	0.01	0.00	0.37	0.02	0.17
Walking speed	40	0.72±0.83	1.21±1.11	1.66±0.82	2.21±0.88	8.21	0.12	0.02	0.04	0.03	0.01	0.16
Gait	40	0.64±0.78	0.82±0.37	1.91±0.55	2.16±0.57	42.91	0.01	0.00	0.00	0.27	0.01	0.12

Remarks: P1: comparison of before treatment and group1; P2: comparison of before treatment and group2;
P3: comparison of before treatment and group3; P4: comparison for group 1 and group 2;
P5: comparison for group 1 and group 3; P6: comparison for group 2 and group 3.

Table 4 PRS score comparison before and after Lantox treatment by different dosage after three month

Items	n	Before (x±s)	Group1 (x±s)	Group2 (x±s)	Group3 (x±s)	q	P1	P2	P3	P4	P5	P6
Flection	40	0.66±0.82	0.98±0.68	1.82±0.91	2.02±0.86	31.02	0.05	0.00	0.00	0.03	0.00	0.00
Talipes equines	40	1.74±0.45	1.76±0.33	2.01±0.63	2.12±0.73	6.11	0.08	0.10	0.08	0.04	0.05	0.06
Back foot	40	1.22±1.02	1.71±1.03	1.88±1.35	2.87±0.90	11.26	0.03	0.00	0.00	0.32	0.00	0.01
Back knee	40	1.44±1.09	1.67±1.05	1.92±8.07	2.36±1.53	5.82	0.07	0.06	0.00	0.37	0.02	0.17
Walking speed	40	0.72±0.83	1.12±1.01	1.66±0.93	2.28±0.91	8.15	0.40	0.05	0.00	0.08	0.02	0.06
Gait	40	0.64±0.78	0.66±0.83	1.91±0.87	1.16±0.88	6.66	0.10	0.06	0.00	0.05	0.01	0.12

Remarks: P1: comparison of before treatment and group1; P2: comparison of before treatment and group2;
P3: comparison of before treatment and group3; P4: comparison for group 1 and group 2;
P5: comparison for group 1 and group 3; P6: comparison for group 2 and group 3.

Table 5 PRS score comparison before and after Lantox treatment by different dosage after six month

Items	n	Before (x±s)	Group1 (x±s)	Group2 (x±s)	Group3 (x±s)	q	P1	P2	P3	P4	P5	P6
Flection	40	0.66±0.82	0.11±0.73	1.71±0.82	2.31±0.971	43.10	0.00	0.00	0.00	0.03	0.00	0.00
Talipes equines	40	1.74±0.45	1.80±0.86	2.07±0.89	2.61±0.99	7.92	0.67	0.20	0.00	0.03	0.00	0.58
Back foot	40	1.22±1.02	1.71±1.06	1.95±1.62	2.21±0.86	6.32	0.05	0.56	0.07	0.32	0.00	0.06
Back knee	40	1.44±1.09	1.73±1.21	1.99±1.13	2.32±0.87	6.76	0.08	0.05	0.53	0.11	0.02	0.21
Walking speed	40	0.72±0.83	1.10±1.01	1.21±0.85	1.68±0.94	9.02	0.40	0.00	0.10	0.08	0.01	0.06
Gait	40	0.64±0.78	1.68±0.86	1.93±0.65	2.12±0.69	5.63	0.06	0.05	0.06	0.27	0.01	0.08

Remarks: P1: comparison of before treatment and group1; P2: comparison of before treatment and group2;
P3: comparison of before treatment and group3; P4: comparison for group 1 and group 2;
P5: comparison for group 1 and group 3; P6: comparison for group 2 and group 3.

Discussion

This clinical study involved the treatment of 120 children by local injection of Lantox. Referring to the experiences of other countries and ours, use hand to localize the muscle position was more accurate. Due to disinfection reason, we did injection only for the undetectable muscle under ultrasound B. This could obtain more satisfactory result. Since there were many injection points, the injection could not proceed under guidance of electromyography. All the patients had different extends of improvement after treatment. The most obvious were improvement of flection of joints and ground touching of heel. 4 criteria (talipes equines, back foot, back knee, walking speed) out of six showed no marked improvement when 1μ/kg was injected but obvious improvement of all 6 criteria was observed when 3μ/kg was injected (Table p3). The back foot had no marked improvement when 1μ/kg was injected but showed marked improvement when dosage was increased to 2μ/kg (Table p2). Back knee and walking speed had obvious improvement when 2μ/kg was injected but the extends of improvement did not increase with dosage. Gait showed obvious improvement for 1μ/kg, 2μ/kg, 3μ/kg injection and might due to good location of gastrocnemius muscle and soleus muscle. The gradient dosage for 1μ/kg-2μ/kg and 2μ/kg-3μ/kg had no significance difference in 4 out of 6 criteria (p4, p5) but obvious difference for 1μ/kg-3μ/kg (p3, p6). This revealed that application of higher dosage was better than lower dosage. Posture improved quickly after Lantox treatment but walking speed improved after one week of injection or even longer. Lantox injection lowered the muscle contraction and rebalanced the muscle movement, so muscle improvement needed some time to occur after adjustment and practice. One month after injection,

the walking speed showed more improvement because of practice and result was similar at two months' time (Table 2 and 3). At three months' time, the efficacy for the gait of group 1 decreased but no change for other criteria. This showed that little dosage had unsatisfactory result and also short duration of improvement. After six months of treatment, the follow-up cases for group 1, 2 and 3 were 31, 23 and 26 respectively. Other cases lost contact. Except flection, talipes equines and walking speed, other criteria showed different extents of decrease in treatment efficacy. The long duration of improvement occurred in cases with regular practice of muscle (3 cases in group 1; 7 cases in group 2 and 11 cases in group 3). This revealed that regular practice of muscle after Lantox injection could improved the muscle movement and lengthened the improvement duration. This could post-phone re-injection and reduced drug tolerance. The gait of group 1 showed most obvious decrease of treatment efficacy.

Longer duration of improvement could result when younger children was treated. The smallest children patient was 16 months old. It required further investigation for the reason that the immune mechanism might be not yet matured in the small children. Theoretically, there was an advantage for the development of bone, muscle movement and mental after improvement of muscle strength in the younger age children. However, since re-injections could result in drug tolerance, the most suitable age for treatment required further investigation. The onset for improvement after injection was mainly between 36-72 hours. One fourteen year old children showed marked improvement in tenth day after injection and this might also show that older the age, longer the onset time.

After treatment, the children patients could walk with heel touched on the ground and the spasmodic muscle could be released. Walking for the children was easier and they were also encouraged mentally.

To conclude, this clinical study proved that, it is better to use higher dosage (2μ/kg, 3μ/kg) of Lantox to treat children cerebral palsy rather than using lower dose (1μ/kg) and the duration of improvement lasted longer. High dose injection and reinjection were the reason for corresponding anti-body production and drug tolerance. However, for the reason of the efficacy, duration of treatment, application of higher dose was still recommended within a proper range. There was no side effect occurred for 6μ/kg injection.

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